

Issue Summary
Blood Products Advisory Committee
June 19-20, 2003

Topic III: Standards for Recovered Plasma

Issue:

Current standards for Source Plasma and recovered plasma are inconsistent creating potential for inappropriate use of recovered plasma that is unsuitable for the further manufacture of some products.

Background:

Recovered plasma is a by-product derived from Whole Blood collection and is distinguished from Source Plasma by the mode of collection and the requirements for storage, pooling, dating and labeling of the product. Recovered plasma may be separated from individual units of Whole Blood by aseptic techniques up to 5 days after expiration or obtained from Fresh Frozen Plasma (FFP) that has expired. Recovered plasma has no expiration date and may be stored either in a frozen or liquid state. The storage and shipping conditions for the product are dictated by the short supply agreement between the recovered plasma manufacturer and the consignee. The time to freezing for these products varies by collection facility but common practices include within 8 hours, 24 hours, or 120 hours of collection.

In contrast, Source Plasma is a licensed product, collected by plasmapheresis (usually using automated apheresis equipment at volumes significantly larger than that of recovered plasma) and frozen immediately after collection. Irrespective of the lack of standards for recovered plasma and the requirements that are in place for Source Plasma, both products are used for further manufacture into the same final products (i.e., IVIG, Factor VIII, IVD components, etc.)

Presently there are 4 citations in the CFR that relate to recovered plasma. These are:

- ?? 606.100(b)(18) – [SOP] Procedures for preparing recovered plasma, if performed, including details of separation, pooling, labeling, storage, and distribution.
- ?? 606.121(e)(5) – Recovered plasma labels shall include:
 - (i) In lieu of an expiration date, the date of collection of the oldest material in the container.
 - (ii) The statement: “Caution: for further Manufacturing Use Only”; or “Caution: For Use in Manufacturing Nonjectable Products Only”, as applicable
 - (iii) For recovered plasma not meeting the requirements for manufacture into licensable products, the statement “Not for Use in Products Subject to License Under Section 351 of the Public Health Service Act.”
- ?? 606.160(b)(2)(iii) – [Records] Separation and pooling of recovered plasma

?? 606.106(d) – [Records] When there is no expiration date, records shall be retained indefinitely.

To allow recovered plasma to be shipped in interstate commerce the manufacturer must comply with the requirements for products deemed to be in short supply as set forth in Title 21, Code of Federal Regulations, Section 601.22 (21 CFR 601.22). To use the short supply provisions, the licensed manufacturer of the final biological product (i.e., licensed fractionator) must have in place with their supplier “... such procedures, inspections, tests or other arrangements as well as assure full compliance with applicable regulations...”

Historically there have been compliance issues associated with recovered plasma due to a lack of consistency in the development of standard operating procedures among establishments manufacturing recovered plasma, the complexity of donor screening procedures, infectious disease testing requirements, labeling requirements, storage and shipping requirements defined under short supply agreements, the inadvertent release of inappropriate units of recovered plasma for further manufacture. Blood establishments that manufacturer recovered plasma must ensure that the plasma is collected from normal healthy donors who meet all donor suitability requirements. Keeping track of appropriate units for disposition can be a daunting task if the facility uses plasma from autologous collection for this purpose. The facility must ensure that the autologous donors are screened with the same medical history questionnaire used to screen allogenic donors, not an abbreviated questionnaire that is usually used for autologous collections, and that the autologous donors have met all other suitability requirements including the hemoglobin determination. The only exception to the donor suitability requirements that FDA has permitted has been the use of the plasma collected from autologous donors who donate more frequently than once in an 8 week period. FDA also requires that all appropriate infectious disease testing be performed, and found negative or non-reactive for each unit of recovered plasma to be used for further manufacture into injectable products with the exception of Hepatitis B Core antibody (anti-HBc) and HTLV I/II. The blood establishments must have procedures in place to ensure that units of plasma not suitable for further manufacture into injectable products are not released for that purpose.

Discussion:

In an effort to address concerns of deficiencies encountered over the years with the preparation, shipment, and use of recovered plasma FDA presented the topic of whether standards governing the manufacture and shipping of recovered plasma should be developed to BPAC on June 13, 2002. The Committee voted unanimously in favor of developing standards including conditions regarding storage, labeling, and expiration as such standards would provide a basis for FDA oversight and would allow for the manufacture of a more consistent product. The Committee recommended that an alternative name that does not have a negative connotation be developed to replace the current name “recovered plasma” and that the designated “intended use” distinction for labeling Source Plasma at the time of collection be removed to allow Fresh Frozen Plasma (FFP) collected by apheresis to be relabeled for further manufacturing use prior to its 1 year outdate. This relabeling provision will pertain to FFP collected by apheresis as

a single component, plasma collected concurrently with other blood components, and to plasma separated from the collection of Whole Blood.

Over the past year FDA has considered these recommendations and is working on developing standards for recovered plasma. To address the recommendation regarding the name of the product FDA suggests that the term recovered plasma be changed to “component plasma” which will be defined as plasma that is collected manually or by apheresis, either separately or concurrently with other blood components, from donors who meet all Whole Blood donor suitability requirements. In order to address the “intended use” distinction regarding Source Plasma, FDA is considering moving the requirement for freezing Source Plasma immediately after filling the final container into the definition of Source Plasma, thereby keeping Source Plasma a distinct product while allowing plasma regardless of its collection method, but frozen within a specific time frame to be relabeled as component plasma for further manufacture. As part of its deliberations, FDA is also considering whether a “time to freezing” standard should be defined for component plasma used to manufacture labile plasma products (i.e. Factor VIII). While the actual definition of such standard is beyond the scope of the current discussion, FDA is seeking Committee comment on the need for such a standard and for labeling categories that would indicate whether the intended use of the component includes labile products.

Questions for the Committee:

With these considerations in mind FDA is seeking advice from the committee on the following issues:

1. Does the Committee agree with defining a new licensed component called “component plasma”?
“Component plasma” would include the products currently called recovered plasma, as well as apheresis plasma collected from allogenic Whole Blood donors, converted unexpired and expired FFP collected by automated apheresis methods, and plasma collected concurrently with other apheresis components.

1(a) Should a different name be applied to plasma intended for manufacturing only into non-injectable products (e.g. reagent plasma) ?
2. Does the Committee agree with changing the definition of Source Plasma in the regulations to include the requirement for freezing immediately after collection?
3. Should the dating period of Component Plasma be uniform at 10 years or specified on the basis of freezing temperature?
4. Should FDA limit use of Component Plasma to make injectable products based on the time to freezing?